Near adult height in girls with idiopathic central precocious puberty treated with GnRH analogues

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ABSTRACT

INTRODUCTION: GnRH analogues (GnRHa) are the treatment of choice in idiopathic central precocious puberty (CPP) thought the real benefit on height gain is unclear. Hence, defining their effect on near adult height (NAH) in girls with idiopathic CPP is the main study's aim.

METHODS: An observational longitudinal prospective descriptive study of a cohort formed by 500 girls included in the Spanish register diagnosed of idiopathic CPP between January 2008 and January 2019 has been carried out. Triptorelin 3.75mg have been monthly administered and the gap between NAH and TH is the primary outcome.

RESULTS: Data at treatment's cessation from 283 girls and at NAH from 132 girls is reported. The primary outcome's mean and 95% confidence interval have been -1,033±6.362 cm and -2.293-0.277 cm respectively.

CONCLUSIONS: GnRHa are helpful in preserving the genetic growth potential as a non-insignificant quantity of patients has reached a NAH close to their TH.

RESUM

INTRODUCCIÓ: Els anàlegs de la GnRH (aGnRH) són el tractament d'elecció en la pubertat precoç central idiopàtica (PPCI). El benefici real sobre l'estatura final és incert. L'objectiu principal de l'estudi és definir l'efecte dels aGnRH sobre la talla quasi final adulta en nenes amb PPCI.

METODOLOGIA: Estudi observacional, descriptiu, longitudinal i prospectiu d'una cohort de 500 nenes incloses en el registre espanyol i diagnosticades de PPCI entre gener'2008 i gener'2019. S'ha administrat Triptorelina 3.75 mg mensualment i la diferencia entre la talla quasi final adulta i la talla diana n'és la variable principal.

RESULTATS: Es reporten els resultats de 283 nenes al final del tractament i de 132 a talla quasi final adulta. La mitjana i l'interval de confiança al 95% de la variable principal són -1,033±6.362 cm i -2.293-0.277cm respectivament.

CONCLUSIONS: Els aGnRH són útils en preservar el potencial genètic de creixement. Una quantitat significativa de pacients ha assolit una talla dins seva talla diana.

RESUMEN

INTRODUCCION: Los análogos de la GnRH (aGnRH) son el tratamiento de elección en la pubertad precoz central idiopática (PPCI). El beneficio real sobre la estatura final es incierto. El objetivo principal del estudio es definir su efecto sobre la talla casi final adulta en niñas con PPCI.

METODOLOGIA: Estudio observacional, descriptivo, longitudinal y prospectivo de una cohorte de 500 niñas incluidas en el registro español y diagnosticadas de PPCI entre enero'2008 y enero'2019. Se ha administrado Triptorelina 3.75 mg mensualmente y la diferencia entre la talla casi final y la talla diana es la variable principal.

RESULTADOS: Se presentan los resultados de 283 niñas al final del tratamiento y 132 niñas en la talla casi final. La media y el intervalo de confianza al 95% de la variable principal son -1,033±6.362 cm y -2.293-0.277 cm respectivamente.

CONCLUSIONES: Los aGnRH son útiles en preservar el potencial genético de crecimiento. Una cantidad significativa de pacientes alcanzan una talla final próxima a su talla diana.

KEYWORDS

KEYWORDS: Idiopathic central precocious puberty, GnRH analogues, Near adult height and target height.

PARAULES CLAU: Pubertat central precoç idiopàtica, anàlegs de la GnRH, talla quasi final adulta i talla diana.

PALABRAS CLAVE: Pubertad central precoz idiopática, análogos de la GnRH, talla casi final adulta y talla diana.

ABBREVIATIONS

- BA: Bone age
- BMI: Body mass index
- CA: Chronological age
- CPP: Central precocious puberty
- FSH: Follicle-stimulating hormone
- GnRH: Gonadotropin-releasing hormone
- GnRHa: Gonadotropin-releasing hormone analogues
- GV: Growth velocity
- HPG axis: Hypothalamic pituitary gonadal axis
- LH: Luteinizing hormone
- NAH: Near adult height
- PAH: Potential adult height
- PP: Precocious puberty
- SD: Standard deviation
- TH: Target height

CONTENTS

1. INTRODUCTION

1.1 THEORETICAL FRAMEWORK

Puberty is a period in which so many physical, hormonal and psychological changes occur due to the hypothalamic-pituitary-gonadal (HPG) axis reactivation *(Annexes: Figure 1)*. Gonadotropin-releasing hormone's (GnRH) pulsatile hypothalamic secretion stimulates gonadotropin (LH – Luteinizing hormone and FSH – Follicle-stimulating hormone) excretion by anterior pituitary gland. As a consequence, the gonadal steroids (testosterone and estradiol) produced induce puberty changes (breast and testicular maturing, majora and minora labia enlargement, body fat increase and redistribution, cricoid cartilage growth, facia hair development, muscle mass increase, growth acceleration…). However, this is a multifactorial process influenced by genetic, environmental, ethnic, metabolic, economic, geographic… factors (1,2).

The development of secondary sexual characteristics (II breast development's Tanner stage) before the age of 8 years or menarche before the age of 9 years in girls is named precocious puberty (PP). In the same way, the appearance of a testicular volume greater than 4 ml before the age of 9 years is considered PP in boys (1–5). It occurs in out 5000 children, being 10 times more frequent in females than in males. According to its physiopathology, PP is classified in diferent categories (1,5–7):

- Normal puberty's variants such as isolated forms of premature telarche, pubarche or vaginal bleeding.
- Peripheral PP: It is gonadotropin-independent as it is caused by a distrubance outside HPG axis like adrenal tumors, germ cells hCG secretory tumors, congenital adrenal hyperplasia, exogen source of gonadal or adrenal hormones…
- Central precocious puberty (CPP): It is the most frequent one and it is a consequence of an early HPG axis reactivacion due to diferent causes (*Annexes: Table 1*). The

idiopathic form is the most common one, being approximately the 90% in girls and the 70% in boys.

The premature sex steroid hormone's secretion that takes place in PP advances the secondary sexual characteristics' progression and increases growth velocity, driving to an early fusion of the long bones' epiphyseal growth plates, resulting in a short stature in comparison with the genetic potential. Besides, this can lead to psychosocial maladjustment (2,4,5,7,8).

GnRH analogues (GnRHa) are the treatment of choice since 1980s in children with CPP (4,7–10). This synthetic decapeptide derives from a chemical substitution of the native molecule, which increases its resistance to enzymatic degradation (2). They compete with GnRH endogenous for its receptor in the anterior pituitary gland, promoting its endocytosis and producing a receptor down-regulation (1). Thus, GnRHa administered chronically suppress sexual hormones' production, reducing growth velocity (GV) and giving to the long bones more time to lengthen before epiphyseal fusion. As a result, the bone age (BA) is progressively normalized and the linear growth continues, so children with CPP can achieve an adult height according with their genetics (4,6,7,11,12). Perhaps, the treatment's main aims are interrupting sexual maturation until pubertal age, stabilizing the sexual secondary characteristics, restoring genetic height potential by delaying skeletal maturation and preventing psychological problems (1,3,9). Depot subcutaneous formulations monthly or trimonthly administered are the preferred ones because of the better patient's compliance. Nevertheless, a prolonged action subdermal implants are available too, even though their use is still controversial (1,2,10,13). Moreover, GnRHa are generally well tolerated, being the local adverse effects related to its injection such as allergic reactions or sterile abscess the most frequent ones. Headache, abdominal pain, vaginal bleeding after the first dose and vasomotor symptoms have been also described,

as well as anaphylaxis, which is extremely rare (1,2,10,13). In addition, body mass index's (BMI) transitional changes and a polycystic ovary syndrome prevalence's increase have been revealed despite the evidence is not conclusive (3,11,14,15).

In relation to the studies made in children, progressive PP forms (defined as the progression from one Tanner stage to another in less than six months and a GV above 6 cm/year), a predicted adult height (PAH) below 2.5 percentile or below target height (TH), a height's standard deviation (SD) below -2 or a PAH loss during a follow up period are treatment indications, as evidence has shown a GnRHa benefit in preserving the genetic height potential, mainly in those girls who had started the treatment before the age of 6 (1,2,11–13,16). On the contrary, results in older children and in non-progressive or slowly progressive PP are not highly convincing. Similarly, no benefits in height gain have been demonstrated in early puberty (defined as pubertal development between 8 and 9 years in girls) (1,2,11,15,16).

1.2 STUDY's JUSTIFICATION

The evidence, which is rich in girls but sparse in boys, seems to demonstrate a GnRHa favorable effect on stature growth thought the net height gain, the effect on BMI or the moment when treatment should be stopped remain debated. These uncertainties come from the lack of large sample sizes prospective studies and randomized control trials in this filed. Besides, historical cohorts reported decades ago are the control group in some studies which also include a low number of subjects and have some methodological limitations (1,2,6,7,9,16,17). In conclusion, more studies are needed to assess the real GnRHa influence on height gain.

1.3 OBJECTIVES and HYPOTESIS

The present study's main aim is to define GnRHa effect on near adult height (NAH) in girls with idiopathic CPP. In addition, describing the mean treatment duration, the

chronological age (CA) and the bone age (BA) at treatment's cessation, the mean time until menarche after therapy's stop, the growth and BMI evolution and the adverse effects registered are the secondary objectives. In conclusion, the study's hypothesis is that GnRHa have a beneficial effect on NAH in girls with idiopathic CPP.

2. METHODS

2.1 STUDY's DESIGN

This is an observational longitudinal prospective descriptive study of a cohort formed by 500 girls from 55 Spanish centers diagnosed of idiopathic CPP and included in the Spanish register (*www.seep.es/pubere)* between January 2008 and 31st January 2019.

2.2 PARTICIPANTS

The inclusion criteria are female sex, the presence of progressive thelarche before *8* years of age, a LH peak more than 7 U/L in LHRH stimulation test (100µg/m^2), a difference between BA and CA of more than 1 year and a normal cranial image. On the contrary, early puberty forms and CPP with an identified etiology are the exclusion criteria.

2.3 INTERVENTIONS and FOLLOW-UP

Girls included have been treated with Triptorelin (GnRHa) 3,75 mg monthly administered, adjusting dose, if necessary, according to LHRH test and evolution. Besides, the follow-up has consisted in a visit and exploration of weight, height, BMI and secondary sexual characters every 6 months and an annually BA evaluation until girls have reached NAH.

2.4 STUDY's SIZE

Study's size has not been calculated before starting in order to achieve the maximum size possible, guaranteeing more reliable results than previous researches, which included a low number of patients. Because of that, inclusion criteria have been applied in Spanish

Register database, selecting all the girls who have achieved them. Consequently, the current study's size is 500 girls.

2.5 RISK OF BIAS

In relation to the risk of bias, having no control group for ethical reasons can lead to a selection bias, because of the comparison with historical cohorts. Moreover, an aleatory error is present as in any study, but the fact of comprising a high number of patients decreases its relevance. Finally, overweight at diagnosis and the adoption are CPP's risk factors, being able to act as confounding factors (1–3,11,14,18,19).

2.6 OUTCOMES

According to the study's aims, the difference between NAH and TH is the primary outcome. Moreover, secondary outcomes are the gap between NAH and PAH (an important variable in adopted girls whose genetical potential is unknown), NAH and its standard deviation (SD), the mean treatment duration, the mean time until menarche after treatment cessation's, the BA and the CA at those moment and the difference between height at GnRHa's withdrawal and NAH. Ultimately, BMI evolution during therapy is also a secondary end-point.

2.7 OUTCOMES' MEASURES

Height, NAH, TH and PAH are expressed in centimeters as well as their standard deviations, which have been determined for age and sex in relation to Spanish children population (20). Girls TH has been calculated by subtracting 6.5 cm from the average parental height whereas PAH has been obtained by Bayley and Pinneau method (21). Likewise, the BA has been assessed using a left hand X-ray and comparing it with the standards, following Greulich and Pile method (21,22). Furthermore, NAH has been measured in girls achieving a BA of more than 15 years or a GV less than 2 centimeters/year if menarche has occurred. The treatment duration and the time between

treatment's stop and menarche are expressed in months while the BA and the CA are described in years. Furthermore, secondary sexual characteristics like breast development have been evaluated by a physical exploration and in accordance with Tanner pubertal staging (*Annexes: Table 2*)(23). At last, weight (Kg) and BMI (weight (Kg)/height(cm)^2) have been also determined and compared with Spanish children population (20).

2.8 STATISTICAL ANALYSIS

Data related to subject's baseline characteristics and study's outcomes has been collect using this computer database (*www.seep.es/pubere*). The normal distribution of the baseline characteristics has been apprised observing the histogram's symmetry (Fisher coefficient) and kurtosis (g2 coefficient) and the difference between the mean and the median. In addition, data has been analyzed by SPSS.25 software. Quantitative outcomes are expressed by their mean, median, minimum, maximum, SD and the 95% confidence interval. Otherwise, qualitative variables are represented by their frequencies.

2.9 ECONOMICAL AND ETHICAL ASPECTS

The current study has been approved by Ethics Committee of clinical investigation (Ethics Committee of the Spanish Society for Pediatric Endocrinology (SEEP)) and patient anonymity and personal information have been always protected following Helsinki Declaration. It does not dispose of a control group because of ethical reasons, as the evidenced GnRHa's benefit in height gain. Due to its design, it does not involve any extra economical cost.

3. RESULTS

3.1 FLOWCHART

SEEP register includes 547 girls diagnosed by PP, but only 500 of them reach the study's inclusion criteria. Results are reported at the end of treatment (n=283) and at NAH (n=132) *(Annexes: Figure 2).*

3.2 BASELINE CHARACTERISTICS

The study's patients baseline characteristics are summarized in *Annexes (Table 3, Figure 3 and 4).* There is a 18% of adopted girls, a 11.6% of immigration and a 68,8% of Caucasian population (*Annexes: Figure 3*). The majority of the cohort lives in an urban residence (70,6%) and, in relation to the autonomous community *(Annexes*: *Figure 4*), most of them are from Catalunya (32.8%) and Community of Madrid (22.6%). Family background is present in 19.6% of cases, being unknown in 26,8% of girls. The mean CA and BA at diagnosis is 7,15 ± 1,083 (n=477) and 9,2 ± 1,387 (n=471) years respectively, with an average difference between them of 2,054 ± 0,896 (n=471) years. Moreover, the most frequent Tanner Stages at diagnosis are Stage II (63,4%) and III (28,8%). Furthermore, the average patients' TH is 159,47 ± 5,174 cm (n=389), being its SD -0.31 ± 0,904 cm (n=389). However, 128,25 ± 8,926 cm (n=473) is the mean height at diagnosis, with an SD of 1,59 ± 1,288 cm (n=473), whereas PAH is 160,29 ± 8,518 cm (n=442). In relation to BMI, its diagnosis value is 17,75 ± 2,418 (n=473) and its SD is 0,51 ± 1,165 (n=473).

3.3 OUTCOMES' RESULTS

Study's outcomes statistical analysis is represented in *Table 4 (Annexes).*

As for primary end-point, the mean difference between NAH and TH and between their SDs has been -1,033 ± 6.362 cm (n=102) and -0,178 ± 1,112 cm (n=102), respectively. In the same way, results show a negative difference between NAH and PAH (mean of -

3,093 ± 7,012 cm, n=126) as well as between their SDs (mean of -0,54 ± 1,225 cm, n=126). In addition, the average NAH and NAH's SD has been 156,48 ±7,073 cm (n=132) and -0,822 ± 1,236 cm (n=132).

Besides, treatment's cessation has occurred with a CA of 10,03 ± 1,004 years (n= 283) and a BA of 11,67 ± 0,793 years (n=240). Thus, the mean treatment's duration has been 29,82 ± 14,21 months (n=282) while the average time until menarche has been 13,14 ± 9,74 months (n=210).

Figure 5 (Annexes) and *6 (Annexes)* show height expressed in centimeters and SD at treatment's start, at treatment's end and at NAH. Related to that, a notable height increase has been seen during the therapy and after its cessation, with a mean difference between height at GnRHa's stop and NAH of 11,27 ± 4,896 cm (n=130). Similarly, a height's SD gap between both moments of 1,98 ± 0,871 cm (n=130) has been present. Moreover, *Figure 7 (Annexes)* represents height's continuous evolution, confirming a progressive stature rise with GnRHa and until NAH.

Along with BMI's SD, its average value at treatment's ending and at NAH has been 1,089 ± 1,277 (n=283) and 0,925 ± 1,249 (n=124). Briefly, as *Figure 8 (Annexes)* demonstrates, a BMI's SD increment have occurred between the therapy's start and suspension even though it after has decreased until NAH.

Finally, a 3.4% (n=17) of girls have suffered adverse effects, such as spotting after the first GnRHa dose (1.2%, n=6), vaginal bleeding following treatment's cessation (0.6%, n= 3), headache (0.6%, n= 3), hair loss (0.6%, n=3), local pain at injection's point (0.2%, n=1), emotional lability (0.2%, n=1) and vasomotor symptoms (0.2%, n=1).

4. DISCUSSION

The most relevant strength of this study is its large sample size, being the first research including such a huge cohort of girls with idiopathic CPP. In addition, it has provided information about GnRHa and PP in the Spanish population, which had hardly been investigated before. Moreover, the NAH comparison with TH instead of with PAH avoids the PAH's overestimation that takes in CPP, especially in those patients whose skeletal maturation is markedly advanced. Besides, the number of subjects evaluated at NAH is relatively small as to the number initially included. To put it in another way, there are several patients being follow up whose analysis when NAH will occur will lead to stronger conclusions.

The main debate about GnRHa therapy has concerned on whether they could have a great benefit on NAH, which is compromised in CPP. Because of that, the main study's objective has been describing GnRHa's effect on height gain by the difference between NAH and TH (or PAH in adopted girls) as a primary variable. According to it, although its mean value is a negative one (-1.033 ±6.362 cm), its confidence interval (IC 95% -2.293 – 0.227), its minimum and maximum and the ±5 cm of error that could take place when calculating PAH demonstrate that a non-insignificant quantity of subjects have achieved and overtook their TH, not differing from what happened in other cohorts (2,4,7,15–17). For instance, *Bereket et.al* obtained a mean NAH 1 cm shorter than TH, concluding that GnRHa may not be capable to restore a full genetic height potential when treatment had been started after a certain critical advancement BA. However, they concluded that a difference of 1 cm is not clinically relevant, because it could be related to so many influences (9). Perhaps, the results support our hypothesis about the beneficial GnRHa's effect on the growth. In relation to height evolution (*Annexes: figure 5, 6 and 7*), the study's findings denote a significant difference between the value at diagnosis, at

treatment's cessation and NAH. Historical series of untreated patients reported an average NAH of 152 cm in girls (2,3,7). Despite these data should be interpreted cautiously because of studies' limitations, a higher NAH and NAH's SD has been revealed in the current research. Additionally, there has been an increment between height at GnRHa withdrawal and NAH, highlighting the importance of stopping the therapy at a specific time, giving to the bones enough time to continue growing.

In terms of the BA and the CA at GnRHa's ending, *Guaraldi et.al* obtained an average CA and BA of 11.1 years (IC 95%: 9.4 – 12.7) and 12.4 years (IC 95%: 11.9 – 13.6) respectively, values which differ a bit from ours (2). Likewise, a mean treatment duration of 29.82 ±14.21 months (IC 95 % 28.13-31.51) is reported whereas *Guaraldi et.al* described a 3 year one (2). Besides, 13.14 ± 9.74 months (IC 95% 11.79 – 14.48) has been described between GnRHa's cessation and menarche, close to *Guaraldi et.al* and other observational studies in whose menstruation occurred on average after 12-16 months (IC 95% 2-60)(1,2,11).

As far as BMI is concerned, overweight has been associated with CPP (1,4,18) and historical cohorts and clinical controlled trials have found a BMI increase during therapy, although it has usually normalized thereafter (2,11,15,24). However, some research have postulated that this condition may persist afterwards (11,14). In accordance with the present study, BMI SD at diagnosis has been over reference population and a higher one has been observed at treatment's cessation, not being significantly different from the one at NAH. Above all, GnRHa's influence on this outcome is still controversial, although it does not seem to be a long-term effect in the majority of cases (2,24).

Finally, treatment have been well tolerated and minor adverse effects have been registered as in previous investigations, despite the long-term ones like polycystic ovaries syndrome or infertility have not been reported.

Nevertheless, this study has some limitations. First of all, the lack of a control group for ethical reasons can have led to a selection bias as well as just including girls, because different factors may be at play in boys with CPP. Furthermore, the comparison with historical cohorts should be interpreted cautiously, because of the possible differences related to baseline characteristics, the small sample size, the inclusion criteria… In the third place and even thought the most studies' primary end-point is the difference between NAH and TH, this is not free of biases, because the midparental TH calculation assumes equal contribution of each parents' heights, neglecting the impact of dominant genes from one of them (9). Finally, several confounding factors such as overweight or adoption could influence GnRHa's effect on height gain (1–3,11,14,18,19).

5. DIFUSSION PLAN

This study is going to be continued following up the girls who are actually registered in the database and including new patients diagnosed of CPP if they achieve the inclusion criteria. Moreover, results are going to be actualized every 5 years and presented in SEEP's congresses. At last, data is going to be published when more than 200 girls have reached NAH.

6. CONCLUSIONS

To summarize, the present study's results suggest that GnRHa therapy is helpful in reaching a NAH close to the TH and PAH, being beneficial in preserving the genetic growth potential. Therefore, it supports most of the evidence contrasted.

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ANNEXES

Figure 1: Chronology of sexual maturation and growth spurt during puberty in both genders according to Marshall & Tanner stages (1).

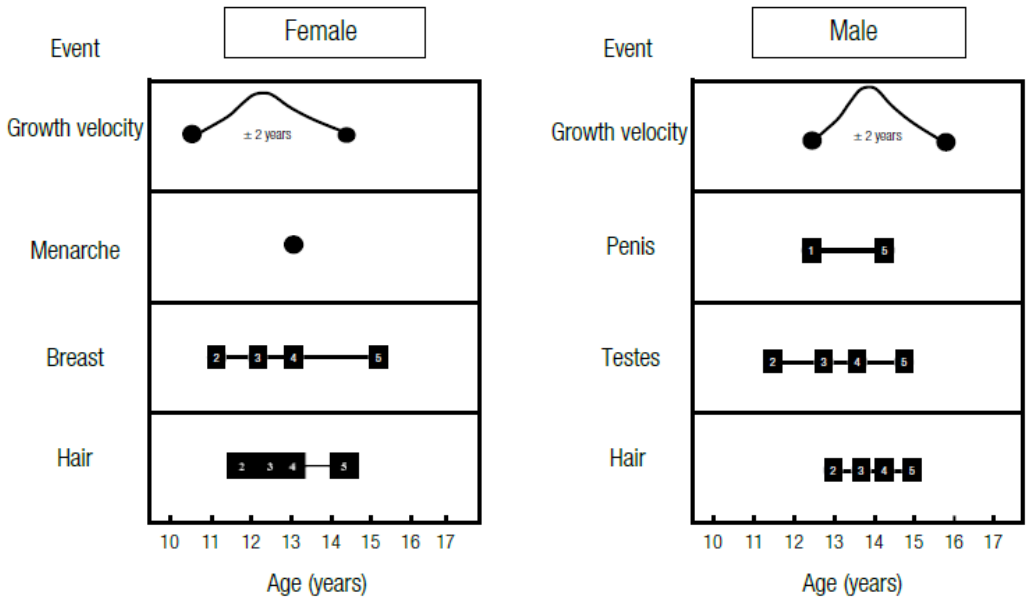

Table 1: Central precocious puberty etiologies (1,5).

CENTRAL PRECOCIOUS PUBERTY ETIOLOGIES	
IDIOPATHIC	
GENETIC CAUSES	Activating mutations in KISS1R and KISS1 genes
	Inactivating mutations in MKRN3 gene
	Chromosomal abnormalities
SECONDARY AND CHRONIC SEX STEROID HORMONE EXPOSURE	Simple virializing congenital adrenal hyperplasia treated lately
	Following resection of sex steroid hormones secretory tumors
	Testoxicosis and McCune-Albright syndrome

INTERNATIONAL ADOPTION	
CENTRAL NERVOUS SYSTEM ABNORMALITIES	Hypothalamic hamartoma
	Pituitary tumors: astrocytoma, ependymoma, hypothalamic glioma, LH-secreting adenoma, pinealoma, neurofibroma, craniopharyngioma, etc.
	Congenital malformations: suprasellar cyst, arachnoid cyst, septo-optic dysplasia, spina bifida, vascular malformations, etc.
	Acquired diseases: inflammatory process (abscess, meningitis, encephalitis, sarcoidosis, tuberculosis), radiation, trauma, perinatal asphyxia.

Table 2: Tanner Breast development stages (23).

TANNER STAGE	BREAST DEVELOPMENT
Stage I	Pre – adolescent; only papilla elevation.
Stage II	Breast bud stage; breast and papilla' elevation as a small mound and areola diameter enlargement.
Stage III	Further breast and areola' enlargement, with no separation of their contours.
Stage IV	Areola and papilla projection to form a secondary mound above the level of the breast.
Stage V	Mature stage; only papilla projection, because of areola recession to the general breast contour

Figure 2: Study flowchart

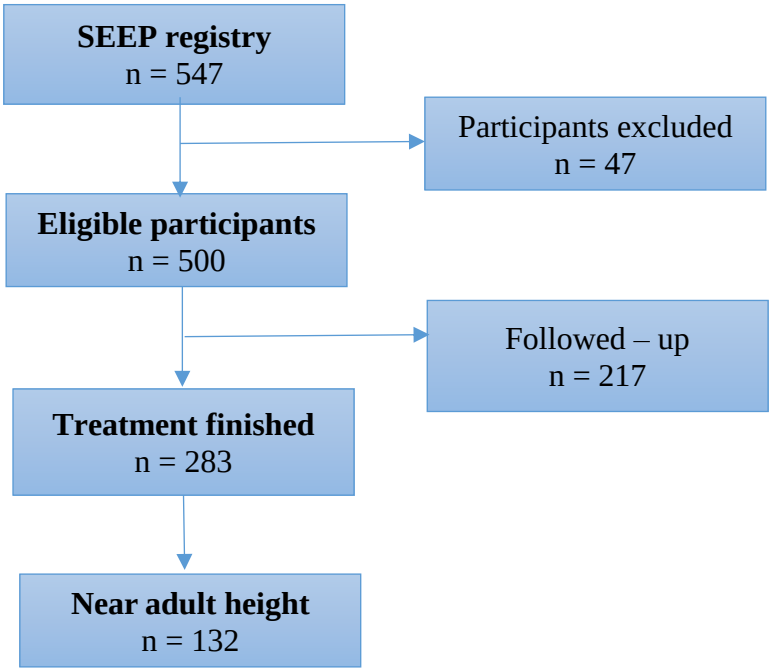

Table 3: Baseline characteristics

Baseline characteristics		N	Frequency	Mean + SD	Median	Minimum - maximum
Adopted	Adopted	90	18%			
	Non - adopted	410	82 %			
Immigration	Immigrant	58	11,6%			
	Non – immigrant	442	88,4%			
Residence	Urban residence	353	70,6			
	Rural residence	147	29,4			
Family background	Yes	98	19,6%			
	No	268	53,6%			
	Non-registered	134	26.8 %			
Tanner Stage	Stage I	4	0,8			
	Stage II	317	63,4			
	Stage III	144	28,8			
	Stage IV	7	1,4			
	Stage V	1	0,2			
	Stage non-registered	27	5,4			
Maternal height (cm)		394		160,15 ± 6,612	160	139 - 190
Paternal height (cm)		390		171,80 ± 7,116	172,00	142 - 192
Born height (cm)		321		48,93 ± 2,66	49,00	34 - 55
Born weight (g)		394		3013,80 ± 562,753	3022,50	770 - 4900
Target height (cm)		389		159,47 ± 5,175	159,5	141,25 – 174,50
Target height SD (cm)		389		-0.31 ± 0,905	-0,31	-3,50 – 2.31
Diagnosis CA (years)		477		7,15 ± 1,083	7,53	1,31 – 9,15
Diagnosis BA (years)		471		9,2 ± 1,387	9	2,5 - 12
Diagnosis BA – CA (years)		471		2,054 ± 0,896	1,96	-0,03 – 7,36
Diagnosis height (cm)		473		128,25 ± 8,926	129,00	81,8 - 153
Diagnosis height SD (cm)		473		1,59 ± 1,288	1,56	-1,74 – 10,48
Diagnosis PAH (cm)		442		160,29 ± 8,518	160,63	133,41 – 189,33
Diagnosis BMI		473		17,75 ± 2,418	17,37	12,37 – 32,83
Diagnosis BMI SD		473		0,51 ± 1,165	0,33	-2,11 – 7,59
LH peak (U/L)		476		21,87 ± 18,801	16,3	7 - 229
LH peak/ FSH peak		465		1,44 ± 1,383	1,125	0,22 – 19,14

Figure 3: Baseline characteristics - Ethnic group

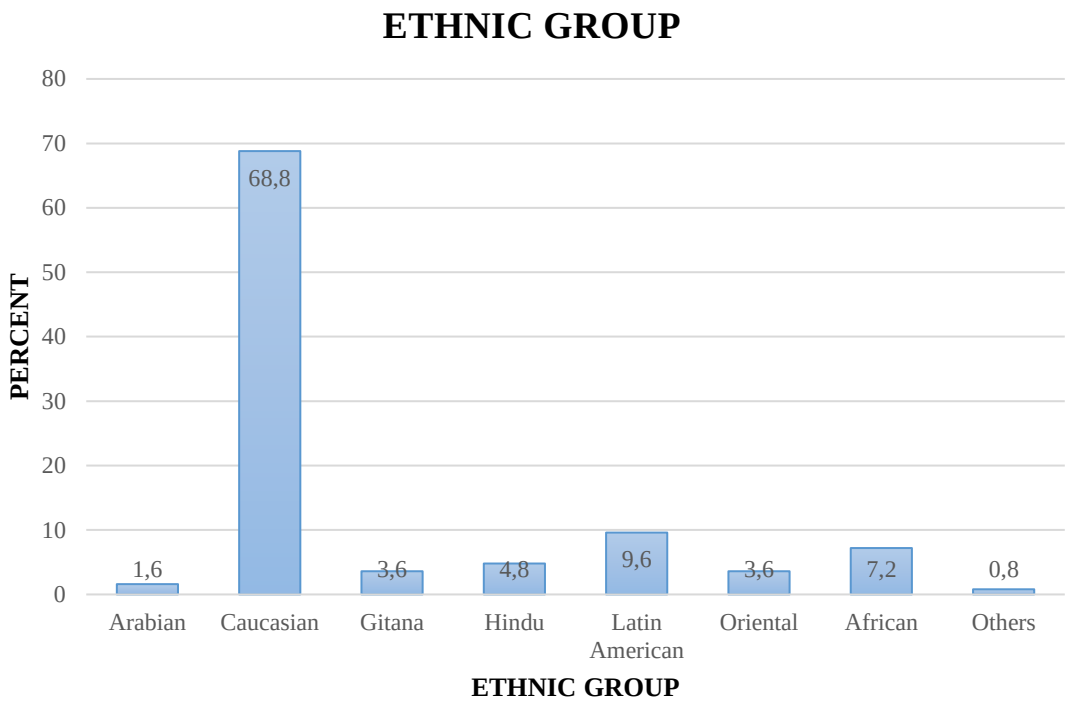

Figure 4: Baseline characteristics - Autonomous community

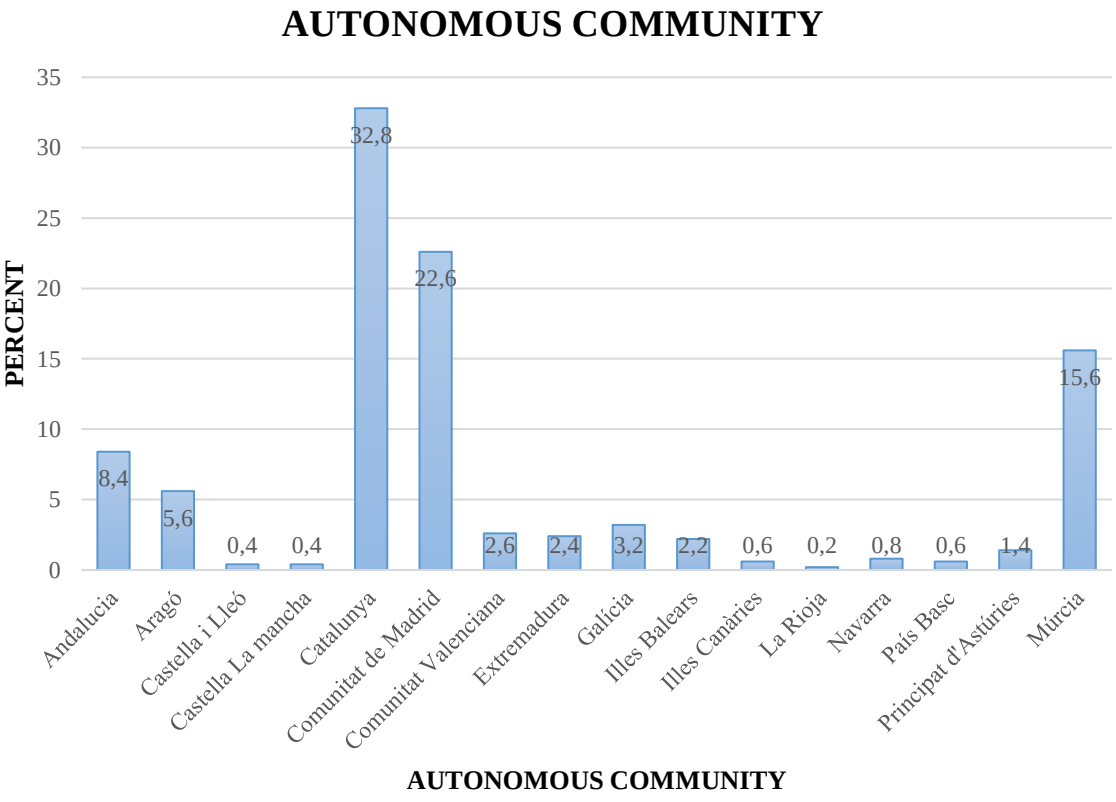

Table 4: Outcomes' results

Outcome	N	Mean ± SD	Median	Minimum - Maximum	IC 95%
NAH – TH (cm)	102	-1,033 ± 6.362	-1,225	-17,50 – 18,00	-2,293 - 0.227
NAH SD – TH SD (cm)	102	-0,178 ± 1,112	-0,215	-3,06 – 3,15	-0,4 - 0,04
NAH – PAH (cm)	126	-3,093 ± 7,012	-3,355	-20,19 – 11,91	-4,344 - -1.844
NAH SD – PAH SD (cm)	126	-0,54 ± 1,225	-0,585	-3,53 – 2,08	-0,759 - -0.322
NAH (cm)	132	156,48 ±7,073	156,6	137,00 – 183,00	155,26 - 157,72
NAH SD (cm)	132	-0,822 ± 1,236	-0,81	-4,24 – 3,80	-1,037 - -0,607
Treatment cessation height (cm)	283	144,88 ± 7,037	144,8	119,4 – 163,3	144,05 - 145,72
Treatment cessation height SD (cm)	283	-2,864 ± 1,231	-2,88	-7,32 – 0,36	-4,327 - -1,4
NAH - Treatment cessation height (cm)	130	11,27 ± 4,896	11,05	0 – 25,00	10,41 - 12,12
NAH SD - Treatment cessation height SD (cm)	130	1,98 ± 0,871	1,935	0 – 4,37	1,83 – 2,135
Treatment cessation CA (years)	283	10,03 ± 1,004	10,055	7,09 – 12,77	9,91 - 10,15
Treatment cessation BA (years)	240	11,67 ± 0,793	11,75	9,75 – 15	11,57 - 11,77
Treatment duration (months)	282	29,82 ± 14,21	28,92	3,70 – 90	28,13 - 31,51
Time between treatment cessation until menarche (months)	210	13,14 ± 9,74	13,56	-34,72 – 49,04	11,79 - 14,48
Treatment cessation BMI SD	283	1,089 ± 1,277	0,96	-1,58 – 5,25	0,94 - 1,24
NAH BMI SD	124	0,925 ± 1,249	0,74	-2,26 - 4,95	0.70 - 1.15

Figure 5: Height's (cm) evolution.

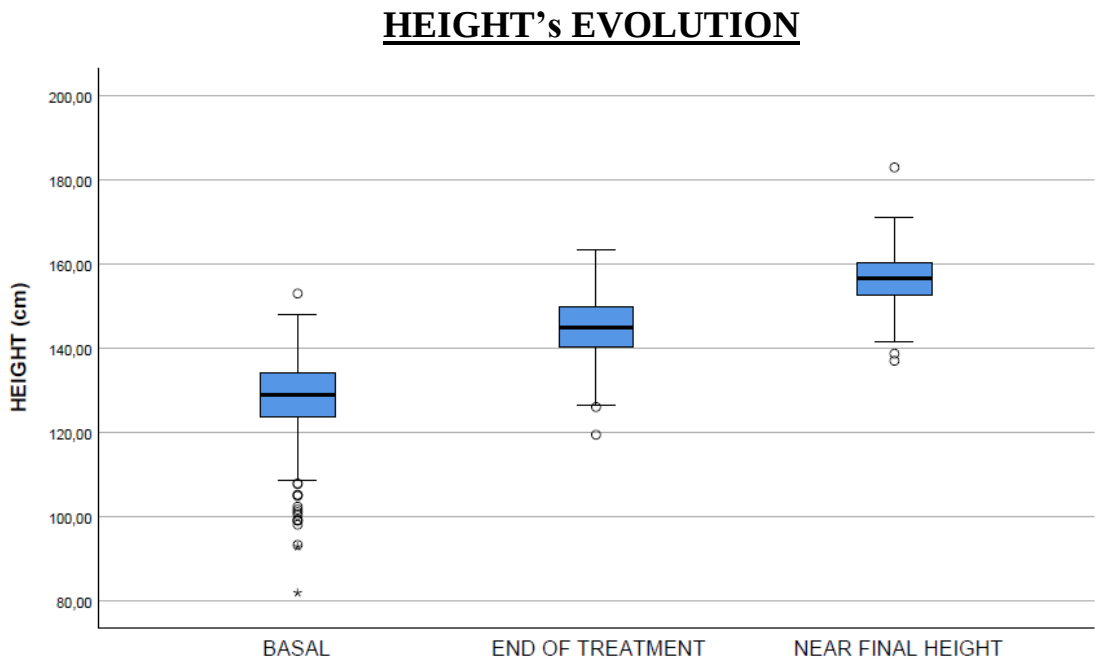

Figure 6: Height's SD (cm) evolution

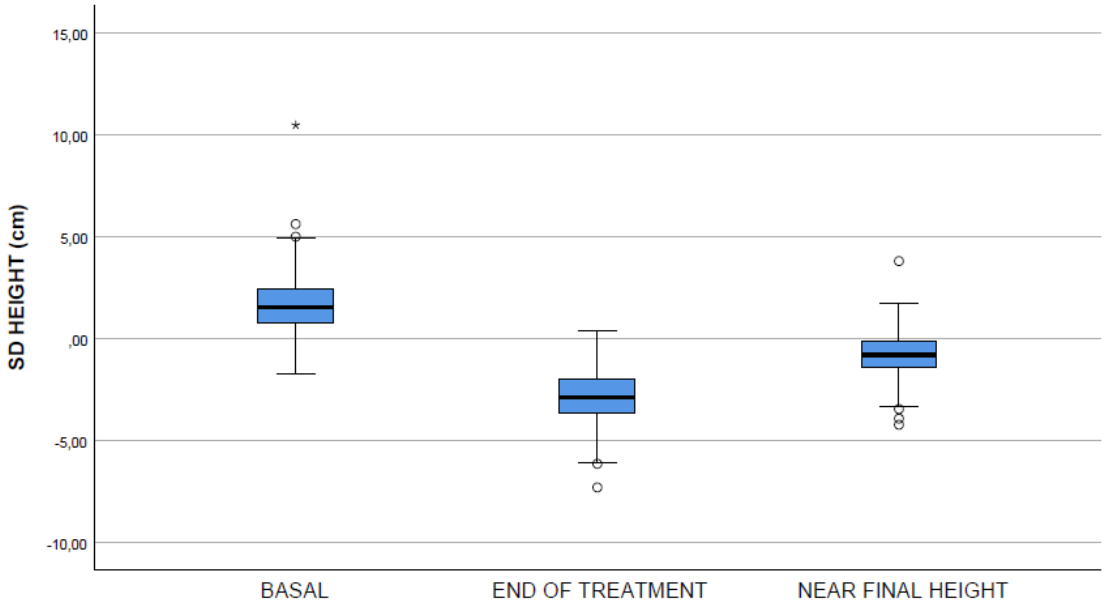

Figure 7: Height's (cm) continuous evolution

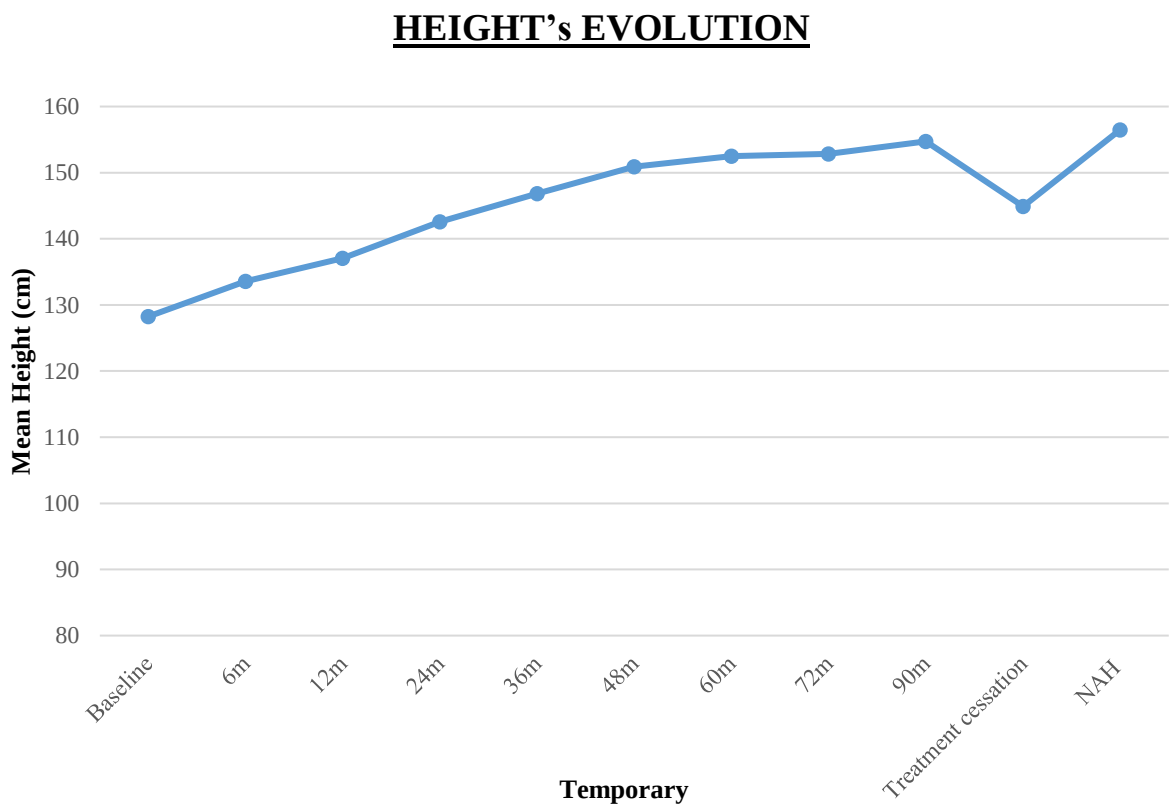

Figure 8: BMI's SD evolution